FEBRUARY 1960

Disease-a-Month

Hyperventilation

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THE YEAR BOOK PUBLISHERS • INC.
CHICAGO

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PRINTED IN U.S.A.

Hyperventilation

EUGENE A. STEAD, JR.

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Eugene Stead Jr.

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WHEN INCREASED VENTILATION occurs without a rise in the pH of arterial blood, the ventilation is said to be compensatory and of a normal volume. When the pH of arterial blood, because of a decrease in CO_2 tension, is increased beyond the level normally found at rest, a state of overbreathing or hyperventilation is said to exist.

Hyperventilation lowers the tension of CO_2 in alveolar air by washing the alveoli more thoroughly with inspired air which contains very little CO_2. The mixed venous blood entering the alveolus by way of the pulmonary artery has been enriched in CO_2 by the metabolism of the tissues. CO_2 passes from the blood into the alveolar air and, because of the rapid rate of diffusion of CO_2 in tissues, the CO_2 tension in the blood and alveolus become equal by the time the blood reaches the pulmonary venous system. Thus, if all the alveoli are ventilated and there is no shunt of blood around the alveoli, either in the heart, great vessels or lungs, the CO_2 tension of pulmonary venous and systemic arterial bloods is equal to that of alveolar air. The CO_2 tension in the venous system is not closely related to alveolar CO_2 tension. It is influenced by the buffering capacity of the blood,

the rate of metabolism in the various organs and tissues, and by the rate of blood flow. The slowest change in ionic balance of blood occurs in the venous blood from the tissues because this change reflects variations in the total buffering capacity of the tissues. Therefore, to establish the diagnosis of alkalosis on the basis of hyperventilation, it is desirable to obtain arterial blood by direct arterial puncture. If one cannot obtain arterial blood, venous blood from a vein draining the skin of the warm hand may be used. The metabolism of the skin is so low in comparison with the rate of blood flow that the blood is nearly arterial in composition. The blood must be handled in a way that will prevent loss of CO_2 and addition of oxygen. The pH of either whole blood or serum and the CO_2 content of serum are measured under anaerobic conditions. The following definitions will be useful.

True plasma or serum. (1) The blood has been collected anaerobically and the serum and plasma separated under oil. (2) The blood has been equilibrated with CO_2 at known tensions and then separated under oil.

Separated plasma or serum. The blood has been drawn and exposed to air. The serum or plasma has then been removed from the red cells.

CO_2 combining power as done in the usual hospital laboratory. Millimols (mM) per liter of CO_2 released by a strong acid from a given quantity of separated plasma or serum which has been equilibrated with CO_2 at a tension of 40 mm. Hg.

CO_2 combining power of true serum or plasma. Millimols per liter of CO_2 released by a strong acid from a given quantity of true serum or plasma which has been equilibrated with CO_2 at a tension of 40 mm. Hg.

CO_2 content of true serum or plasma. Millimols per liter of CO_2 released by a strong acid from a given quantity of true serum or plasma.

Dissolved CO_2. The amount of CO_2 dissolved in plasma, serum

or blood. This varies directly with the pCO_2. The amount of H_2CO_3 in the plasma or serum is not measured. The dissolved CO_2 is in equilibrium with H_2CO_3 in a ratio of 800 to 1. The Henderson-Hasselbalch equation for the $\frac{[HCO_3^-]}{[H_2CO_3]}$ buffer system can be written

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3] + [\text{dissolved } CO_2]}$$

$[HCO_3^-]$. Concentration of bicarbonate ions in millimols per liter. Note that HCO_3^- is an acceptor of protons (H^+) and therefore acts as a base. H_2CO_3 is a donor of protons and, therefore, an acid. $[HCO_3^-]$ is obtained by subtracting the [dissolved CO_2] from total CO_2 in millimols per liter.

CO_2 tension (pCO_2) is measured in mm. of Hg. The CO_2 tension of true plasma or serum is calculated from the pH and CO_2 content. The CO_2 tension of true arterial plasma and serum is equal to the CO_2 tension of alveolar air. Knowing at body temperature the solubility of CO_2 per mm. of CO_2 tension, the millimols of dissolved CO_2 can be calculated.

THE BICARBONATE CARBONIC ACID BUFFER SYSTEM

Because of its ready availability, serum or plasma is usually studied when the question of disturbances in the acid-base equilibrium arises. The pH of extracellular fluid can be defined by the relationship between the bicarbonate and carbonic acid of the serum. At pH of 7.40 the ratio of bicarbonate to H_2CO_3 + dissolved CO_2 is approximately 20:1. As the ratio of dissolved CO_2 to H_2CO_3 is about 800:1, the denominator of this ratio may be taken as the millimols of dissolved CO_2, and the concentration of H_2CO_3 may be disregarded. If the solubility of CO_2 in mM per liter per mm. of Hg in serum at body temperature is designated as "a," the Henderson-Hasselbalch equation may be written as follows:

$$pH = 6.10 + \log \frac{[\text{total } CO_2 \text{ in mM}] - [apCO_2]}{[apCO_2]}$$

From the measured pH and total CO_2 content, the above equation may be solved for pCO_2. pCO_2 times "a" gives the millimols of dissolved CO_2. This, subtracted from the millimols of total CO_2, gives the concentration of HCO_3^-. We now have the bicarbonate-total dissolved CO_2 ratio in millimols per liter.

Because the pH is measured by the $[HCO_3^-]/[\text{dissolved } CO_2]$ ratio, rather than by the concentration of either HCO_3 or dissolved CO_2, the following facts should be noted:

1. The pH of serum cannot be calculated from the CO_2 content of true serum or from the CO_2 combining power of either true or separated serum. Neither of these values, one measuring total CO_2 content in blood drawn under oil to prevent change in CO_2 content, the other measuring total CO_2 content after equilibration of serum with a known concentration of CO_2, divides the CO_2 into its component parts.

2. At any given ratio of $[HCO_3^-]$ to $[\text{dissolved } CO_2]$, the addition of acid or the removal of acid will cause a smaller change in pH when the absolute concentrations of both HCO_3^- and dissolved CO_2 are relatively large. Lowering the concentration of both HCO_3^- and dissolved CO_2 will cause a greater pH shift with the addition or removal of a given quantity of acid.

3. CO_2 is more diffusible than HCO_3^-. For this reason, compensatory changes induced in certain extracellular fluids may occur more slowly than they do in serum. When the CO_2 tension is restored to normal, these tissues may remain acidotic for some time before HCO_3^- returns to the levels present in serum.

4. Acute hyperventilation causes a marked change in pH, a marked lowering of alveolar CO_2 tension and arterial pCO_2, with little change in CO_2 combining power. Different aliquots of arterial blood obtained during acute hyperventilation will give different values for plasma CO_2 combining power, depending on the way the plasma is handled. When whole blood is equilibrated with CO_2 at a tension of 40 mm. Hg and the plasma separated anaerobically, a sample of true plasma is obtained. When whole

blood is separated from plasma without bringing the CO_2 tension back to the average resting alveolar tension of 40 mm. Hg, a sample of separated plasma is obtained. In the presence of hyperventilation, bicarbonate concentration of true plasma is higher than that of separated plasma. The use of separated plasma rather than true plasma may account for the reports of considerable decreases in carbon dioxide combining power with short periods of hyperventilation. As hyperventilation persists, compensatory reactions occur. The arterial pH returns toward normal because $[HCO_3^-]$ decreases. The concentration of sodium falls, that of chloride rises and the CO_2 combining power of true serum is decreased.

5. Respiratory alkalosis can occur over a wide range of concentration of bicarbonate. The bicarbonate may be greatly depressed by the presence of nonvolatile acids. Despite this, the pH of the arterial blood may be alkaline because of an even more marked lowering of dissolved CO_2. In this situation, both the CO_2 content and the CO_2 combining power will be reduced but the pH of arterial blood will be alkaline.

pH, CO_2 TENSION, AND $[HCO_3^-]$ OF SPINAL FLUID

Spinal fluid has a slightly lower pH than arterial blood. The CO_2 tension of spinal fluid is higher than that of arterial blood and the $[HCO_3^-]$ is approximately 1 mM per liter higher. These values indicate that, as might be expected, the spinal fluid is more nearly in equilibrium with the venous blood. Overbreathing on air causes a fall in CO_2 tension and a rise in pH, while increasing the CO_2 tension in inspired air causes a fall in pH and a rise in CO_2 tension in spinal fluid. Thus, the spinal fluid compartment is readily permeable to CO_2 as a gas.

When the pH of arterial blood is reduced for 30 minutes by the administration of ammonium chloride or hydrochloric acid, the spinal fluid becomes more alkaline. The CO_2 tension is reduced by the increase in ventilation but the $[HCO_3^-]$ does not

fall. If the fall in CO_2 tension in the arterial blood is prevented, by keeping the ventilation unchanged by the use of a respirator, the infusion of acid no longer causes the spinal fluid to become more alkaline.

Rapid intravenous infusion of concentrated sodium bicarbonate solution causes an increase in ventilation followed by a fall in breathing. The increase in breathing is accompanied by a fall in pH in the spinal fluid in the face of a high blood pH. The nonmetabolic CO_2 released on the infusion of the bicarbonate diffuses into the spinal fluid and causes the fall in pH. This same rise in CO_2 tension in the blood is accompanied by a rise in pH because the [HCO_3^-] increases more than the [dissolved CO_2]. As the nonmetabolic CO_2 is eliminated, the ventilation is decreased.

The behavior of spinal fluid pH in the presence of varying CO_2 tensions depends on the fact that spinal fluid is readily permeable to CO_2 as a gas but not readily permeable to [HCO_3^-]. The bicarbonate concentration of spinal fluid usually remains constant for at least 1 hour after the concentration of CO_2 in the arterial blood has been changed. Once the [HCO_3^-] has been lowered, a normal tension of CO_2 will cause a rapid rise in the dissolved CO_2 and an acid spinal fluid until the bicarbonate is also increased to the normal level.

These data on the spinal fluid are of interest but they do not necessarily reflect the changes in pH of the cells of the central nervous system which regulate respiration. Consideration of capillary-surface area relationships and of the rate of circulation of the spinal fluid makes it likely that the spinal fluid changes are slower than those of cells.

REGULATION OF RESPIRATION

Breathing is regulated by changes in the arterial blood perfusing the respiratory center or centers in the brain, and by stimuli fed into the central nervous system from peripheral chemosensitive areas, as the carotid sinus, and from all sensory nerves

and sensory areas of the central nervous system. The respiratory center in the medulla is sensitive to changes in pH of arterial blood, and particularly to those changes in pH of arterial blood caused by changes in dissolved CO_2. The sensitivity of the respiratory center to CO_2 is increased when the subject is awake, during pregnancy, after administration of progesterone and after certain types of cerebral accidents. It is decreased by sleep, anesthesia, morphine and by extreme obesity.

The regulation of the quantity of dissolved CO_2 in the arterial blood, the denominator of the Henderson-Hasselbalch equation, is regulated by changes in ventilation. At body temperature, dissolved CO_2 concentration in pulmonary venous blood is determined solely by one consideration: namely, the pressure of the CO_2 gas in the solution. In the absence of shunts, this gas pressure is determined by the alveolar CO_2 tension. By contrast, the HCO_3^- in plasma of arterial blood is regulated by several factors: the CO_2 tension of arterial blood, the presence of nonvolatile acids and bases, shifts of ions between extracellular and intracellular fluid, and excretion of Na, K, and HCO_3 by the kidney.

The chemosensitive areas in the carotid sinuses respond to a change in oxygen tension. A rise in oxygen tension decreases breathing and a fall causes an increase. A decrease in arterial O_2 tension from a lower oxygen tension in expired air, from decreased alveolar capillary permeability, or from a right-left shunt, causes a rise in ventilation from stimulation of the carotid sinus chemoreceptors. The sensitivity of these chemoreceptors is not constant. Changes in oxygen tension of a degree usually associated with only minor changes in respiration may cause an unusually large change in patients who are dyspneic because of heart failure, in normal persons during heavy exercise and in normal persons in the period of hyperpnea caused by the sudden release of cuffs occluding the circulation to both lower extremities.

Increasing the sensitivity of the respiratory center results in an excessive loss of CO_2 and respiratory alkalosis. The overbreathing

causes a rise in arterial oxygen tension. A decrease in oxygen tension of arterial blood from a low O_2 pressure in inspired air, or from a decrease in alveolar pulmonary capillary permeability, increases the ventilation. This raises the alveolar O_2 tension but lowers CO_2 tension, and respiratory alkalosis results.

After prolonged hyperventilation in a respirator or after marked prolonged lowering of CO_2 content by diabetic acidosis or salicylate intoxication, the respiratory center appears to become more sensitive to a given tension of CO_2. In the recovery phase from both diabetic acidosis and severe salicylate intoxication, patients usually go through a period of respiratory alkalosis. It may be difficult to remove a patient from a respirator if chronic overbreathing has been present because he may be uncomfortable unless he can maintain the low CO_2 tension to which he has become accustomed. All of the factors determining this change are not known, but some are. As the pH of the arterial blood is determined by the $[HCO_3^-]$ $[H_2CO_3]$ ratio and as the $[HCO_3^-]$ is depressed in chronic respiratory alkalosis and in the recovering phase of metabolic acidosis, a normal quantity of $H_2CO_3^-$ resulting from the average CO_2 tension will cause acidosis and stimulation of the respiratory center. In chronic respiratory acidosis, the bicarbonate concentration of blood and spinal fluid is increased. A given rise in CO_2 tension in the arterial blood causes a smaller fall in spinal fluid pH than in a normal subject because of the increased concentration of $[HCO_3^-]$.

Metabolic alkalosis does not depress respiration to the degree that one would expect from the marked increase caused by acidosis. The diagnosis of metabolic alkalosis is not made clinically from respiratory depression. In controlled studies, alkalosis does cause a measurable reduction in ventilation. The response to the rapid infusion of $NaHCO_3$ is particularly interesting. During rapid infusion of hypertonic bicarbonate solution, the arterial pH, arterial and alveolar pCO_2, total ventilation and rate of elimination of CO_2 are significantly increased above control levels. Dur-

ing this phase, the spinal fluid becomes more acid. The stimulation of respiration is caused by the intravascular formation of excessive carbonic acid by reaction of infused bicarbonate ion with relatively acid protein buffers of the blood. This nonmetabolic CO_2 is produced as follows:

$$Na^+ + HCO_3^- + \text{buffer} \rightarrow Na^+ + \text{buffer}^- + H_2CO_3$$

$$H_2CO_3 \xrightarrow[\text{anhydrase}]{\text{carbonic}} H_2O + \text{dissolved } CO_2$$

The increased CO_2 content and tension in the arterial blood cause the blood flow to the brain to increase, and the greater diffusibility of CO_2 as compared to HCO_3^- results in a decrease in the bicarbonate:dissolved CO_2 ratio. This is reflected in a fall in pH in the spinal fluid.

In the first hour after infusion of the hypertonic $NaHCO_3$, the pH remains elevated and respiration is slightly depressed. This causes a rise in alveolar CO_2 and arterial tension to compensate for the alkalosis. Other alkalizing solutions do not have the initial phase of respiratory stimulation seen with $NaHCO_3$.

NORMAL VALUES FOR ARTERIAL pH AND CO_2

With the generalized sensory input from the central nervous system and peripheral nerves, and the specialized input from peripheral chemoreceptors modifying the activity of the nervous system, it is not surprising to find considerable variation in the levels of pCO_2 in normal subjects and in the same subject over a period of time. The commonly accepted values of arterial blood are pCO_2 of 40 mm. Hg and a pH of 7.42. The direction of error would be for the patient to overbreathe and to record too high a pH and too low a pCO_2. Studies in normal subjects with inlying arterial needles where the samples can be taken without repeated arterial punctures have in general shown a higher level of pCO_2 (46 mm. Hg) and a lower pH (7.375). With a normal level of bicarbonate, the pH of arterial blood changes approximately 0.01 pH unit with each 1 mm. change in CO_2 tension. During sleep,

the ventilation is decreased and CO_2 tension rises and pH falls. One must either look on normal sleep as representing hypoventilation or on being awake as representing mild hyperventilation. The reaction of the patient to the needle may affect oxygen tension also. A single normal oxygen tension obtained by an arterial puncture does not necessarily mean that the arterial blood is normally oxygenated at the usual level of ventilation.

TYPES AND CAUSES OF HYPERVENTILATION

Hyperventilation can be acute or chronic. In acute episodes of hyperventilation, the pH of arterial blood is raised because of the fall in H_2CO_3. This one measurement lets the physician know that alkalosis is present. If the CO_2 content of the arterial serum is increased, metabolic alkalosis is present. If the CO_2 content of the arterial serum is decreased, respiratory alkalosis and, by definition, hyperventilation are present.

In chronic forms of hyperventilation, the pH of the arterial blood approaches normal because of compensatory responses. The resting volume of ventilation is increased, the CO_2 content of the serum is decreased, and the serum chloride concentration is increased. The subject is asymptomatic.

Hyperventilation may be caused by:

1. Voluntary increase in rate and depth of breathing.
2. Involuntary increase in rate and depth of breathing in the absence of any recognizable disease state.
3. Increase in volume of ventilation by use of respirator.
4. Stimulation of respiration by anoxemia.
5. Increased sensitivity of the respiratory center to CO_2 or presence of agents which drive the respiratory center despite a fall in CO_2 tension.
6. Decreased buffering capacity of the body because of a decrease in $[HCO_3^-]$.

CHANGES INDUCED BY ACUTE HYPERVENTILATION EITHER BY VOLUNTARY OVERBREATHING OR USE OF THE RESPIRATOR

General Symptoms

Hyperventilation causes a feeling of lightheadedness and uncertainty in most normal subjects. In some, confusion will develop. Most subjects note a sensation of numbness and tingling about the mouth and over the face, with the same sensation in the extremities. The heart rate increases and the hands and feet become cool. The amount of heat and moisture lost by the overbreathing varies with the humidity and temperature of the respired air. Eventually, frank tetany develops.

Hyperventilation is commonly followed by a period of apnea but some subjects will continue overbreathing after the observer has turned his attention elsewhere. This is more common in patients than in normal subjects, and is usually associated with other symptoms of acute anxiety and frequently with crying.

Tetany

Numbness of the face and lips and tingling of extremities occur in most subjects with hyperventilation. In many subjects, muscle spasms occur. The hands assume the "accoucheur's" position, characteristic of Trousseau's test, and this is not prevented by a tourniquet placed high enough to exclude blood with a low CO_2 concentration from entering the forearm. A positive Chvostek's sign is usually present. The precise cause of tetany is unknown. The total serum calcium is normal and it is assumed that the ionized calcium is reduced because of the alkalosis. Subjects with pH above 7.5 following ingestion of $NaHCO_3$ did not show tetany, whereas subjects made acidotic with NH_4Cl who hyperventilated

developed tetany at pH of 7.5 to 7.55. Some combination of reduced CO_2 tension, increased pH and low calcium ion concentration appear to increase the irritability of nerves to the point of tetany.

CHANGES IN THE CIRCULATORY SYSTEM

Hyperventilation causes a marked rise in heart rate and occasionally precipitates paroxysmal auricular tachycardia. During the first minute the systolic and diastolic pressures fall but these return rapidly to control levels. The blood flow in the hands, feet and brain is decreased. It is increased in the forearm and presumably in other areas having large amounts of muscle. The cardiac output is increased. These effects of hyperventilation must be caused by a summation of several effects. The decrease in cerebral blood flow and the increase in blood flow to the areas comparable to the forearm appear to be direct effects of the lowered CO_2 tension in these parts. The maintenance of the arterial pressure is dependent on the integrity of the autonomic nervous system. The changes in irritability of the nervous system and the alteration in functions of many organs caused by the hyperventilation may produce many indirect effects.

In the presence of an intact nervous system, blood pressure is well maintained when the patient hyperventilates while standing. If the symptoms of the hyperventilation induce anxiety, typical vasodepressor syncope may occur. In these instances, a precipitous fall in arterial pressure occurs and the patient loses consciousness. When the autonomic nervous system has been injured either by disease or ganglionic blocking agents, overbreathing causes a marked fall in systolic and diastolic pressure, which return slowly to normal when the hyperventilation ceases. In these patients, the effects of posture and overbreathing are additive and the blood pressure will be better maintained if overbreathing does not occur.

Standard textbooks of physiology state that a loss of carbon dioxide from the arterial blood causes (1) vasoconstriction by

direct effect on blood vessels and (2) vasodilation through effect on the central nervous system. The central effect is said to be dominant and the over-all result is a fall in peripheral resistance. The observation that decreased function of the autonomic nervous system potentiates the vasodilator effect in man makes one doubt that the over-all effect of carbon dioxide deficit on the blood vessels is vasoconstriction. Detailed studies in normal subjects, in patients with most of the sympathetic ganglia removed, and in patients receiving ganglionic blocking agents, showed that the over-all effect of carbon dioxide deficit in the arterial blood is vasodilation, and that this caused a sustained fall in arterial pressure unless it was counteracted by the normal homeostatic neurogenic mechanisms for maintaining constant arterial pressure. Because of the activity of these regulating mechanisms, the fall in peripheral resistance does not cause a large and sustained fall in arterial pressure.

ELECTROCARDIOGRAM

Hyperventilation causes a flattening of the T waves. This effect is the result of alkalosis and is brought on by alkalosis from the ingestion of alkaline salts. These changes in T waves are not prevented by the inhalation of 100% oxygen or by nitroglycerin. They are prevented by the inhalation of 5% CO_2 and by the administration of potassium. In patients complaining of symptoms caused in part by hyperventilation, the T waves are frequently unstable and show changes with posture as well as hyperventilation.

ELECTROENCEPHALOGRAM

Hyperventilation causes a shift of electrical activity of the cerebral cortex toward large slow potentials. The first slow wave activity appears over a wide range of alveolar carbon dioxide tension in normal subjects. The degree of shift is influenced by the level of blood glucose. Marked lowering of the blood sugar causes

slow activity in the electroencephalogram without hyperventilation. Lowering of the blood sugar to a level producing little change in the electroencephalogram potentiates the effect of hyperventilation. Oxygen tension also has an influence on the electroencephalogram. Hyperventilation with oxygen causes less change than hyperventilation with air, and overbreathing with low oxygen mixtures causes more severe changes than overbreathing with air. In patients with petit mal, a moderate degree of hyperventilation frequently produces large slow waves followed by the characteristic spike and dome pattern.

ACUTE CHANGES IN ARTERIAL BLOOD CAUSED BY OVERVENTILATION

Before describing in detail the effects on the blood of acutely lowering the alveolar tension, let us look once more at the state of the CO_2 which is to be lost. Only one-twentieth of the CO_2 in the plasma is in the dissolved state where it can be readily moved along a gradient established by a fall in alveolar CO_2 tension. The great majority of the CO_2 is in the form of HCO_3^-. It needs a proton to form H_2CO_3 and then must be dehydrated to CO_2. In the absence of some helping hand, this dehydration reaction moves too slowly for much CO_2 to be lost in the time the blood remains in the pulmonary capillaries. The helping hand (carbonic anhydrase) lies in the red cells and therefore most of the CO_2 to be lost must pass through the red cells. The necessary hydrogen ions come from the hemoglobin and the majority of the CO_2 comes from the bicarbonate of red cells and from the bicarbonate of plasma which has diffused into the red cells. The CO_2 is finally lost from the plasma but the red cell is the chief site of the liberation of the CO_2.

A reduction of tension of CO_2 by overbreathing reduces the amount of dissolved CO_2 in the blood and raises the pH of both blood and extracellular fluid. The effect of the loss of CO_2 from the blood is partially buffered by a decrease in bicarbonate in the

plasma. The pulmonary arterial blood arriving at the alveolus gives up CO_2 because of the gradient of pressure between pulmonary arterial blood and the air in the alveolus. CO_2 flows to the alveolar air through the plasma from the erythrocyte. H_2CO_3 is formed from red cell HCO_3^- and from plasma HCO_3^- which moves into the red cells with H^+ made available by the dissociation of the newly formed oxyhemoglobin. Carbonic anhydrase catalyzes the dehydration of the carbonic acid so that CO_2 formed from the HCO_3^- can diffuse out of the erythrocyte through the plasma into the alveolar space. The K^+ ions within the erythrocyte which were previously electrically neutralized by HCO_3^- ions are now neutralized by the oxyhemoglobin. As the $[HCO_3^-]$ decreases in the cells, chloride shifts from cells to plasma. During these changes, the erythrocyte loses and the serum gains water. This is reflected in a fall in hematocrit reading. The electrolyte concentration of arterial serum decreases about 1.7% with hyperventilation.

A second immediate buffering effect of the reduced CO_2 tension is a transfer of Na^+ from the extracellular fluid to the cells in exchange for H^+ and K^+. The H^+ unites with the HCO_3^- to form H_2CO_3 which is dehydrated to CO_2 by carbonic anhydrase and leaves the body as CO_2 and water. The potassium together with an equivalent of HCO_3^- is excreted in the urine.

In the first two minutes of hyperventilation, K^+ enters the blood in sufficient quantity to raise the serum potassium an average of 1.2 mEq./L. During this time, potassium concentration in hepatic venous blood is greater than in arterial blood. Venous blood from the internal jugular and antecubital veins contains less potassium than arterial blood. As hyperventilation continues, potassium levels in the serum fall and urinary excretion rises. The serum phosphorus falls about 0.6 mg. %. As in other forms of alkalosis, the lactic acid concentration in the blood is increased.

CHANGES PRODUCED BY RENAL COMPENSATION

In response to the alkalosis, the kidney increases its excretion of Na, K and HCO_3^-. The potassium excreted comes from the K^+ moving from the cells as Na^+ shifts into them. In prolonged overbreathing with severe salicylate intoxication, the loss of potassium may become a serious problem and potassium replacement a necessary part of therapy. The loss of sodium may be enough to cause a slight fall in serum sodium concentration. The volume of urine is increased and the excretion of phosphate and ammonia is decreased.

The kidney reabsorbs a greater proportion of filtered bicarbonate when the CO_2 tension is increased, and reabsorbs a smaller proportion when CO_2 tension in lowered. This is an ideal arrangement because a rise in CO_2 tension in chronic lung disease results in increased reabsorption of HCO_3^- with a rise in pH toward normal, and a fall in CO_2 tension from overbreathing results in a decreased HCO_3^- reabsorption, with a fall in pH toward normal. It is worth noting that the direction of change in the rate of HCO_3^- reabsorption does not necessarily indicate the directional change in the rate of HCO_3^- excretion. In metabolic alkalosis, the pCO_2 is increased and the rate of reabsorption of HCO_3^- is increased. At the same time, the filtered load is greatly increased and the excretion of HCO_3^- is increased. Thus, in this instance an increased rate of reabsorption is associated with an increased rate of excretion.

The urine in uncomplicated hyperventilation becomes alkaline. In the presence of potassium deficiency or previous loss of sodium from the body, the urine may remain acid.

CHANGES IN CHRONIC HYPERVENTILATION

When patients live at high altitudes, hyperventilation may be present over many years. A given reduction in CO_2 tension in the arterial blood causes much less change in pH because the bicarbonate concentration may fall as much as 8 mEq./L. The

changes in sodium and potassium excretion which are so striking in acute experiments are less marked and are masked by the effects of gastrointestinal intake of these materials. The subjects have no symptoms once they are adapted to the high altitude.

At a given altitude, the alveolar CO_2 tension is always lower and the O_2 tension higher when the subject is acclimatized. At approximately 10,000 feet the ventilation is increased, with acute exposure, approximately 113% of the control value and 133% with chronic exposure. In acute exposure the anoxic drive from the peripheral chemoreceptors is partially counteracted by the alkalosis in the central nervous system caused by the loss of CO_2. After chronic exposure, the bicarbonate falls until the ratio between bicarbonate and dissolved CO_2 returns to normal and the chemoreceptor drive from anoxia is not balanced by alkalotic inhibition of the respiratory center.

In acute exposure to decreased atmospheric pressure, alveolar oxygen tension drops to between 50 and 60 mm. Hg before alveolar CO_2 tension begins to fall. In chronic exposure, the fall in alveolar CO_2 tension begins at alveolar oxygen tension of 100 mm. Hg. On return to sea level, hyperventilation subsides slowly with a gradual rise in alveolar CO_2 levels over a few days. Chronically adapted men have a greater response in ventilation for a given increase in CO_2 concentration in the inspired air.

We have the interesting situation that acute hyperventilation causes apnea and chronic hyperventilation causes increased ventilation. In acute hyperventilation, apnea occurs because the peripheral chemoreceptors are inactive due to the high alveolar oxygen tension, and the respirator center is inactive because of the fall in dissolved CO_2. In acute exposure to high altitude, ventilation is originally increased by the drive from the peripheral chemoreceptors, and the increased breathing, at least in vagotomized dogs, is abolished by blocking the carotid sinus nerve by cold. When hypoxic hyperventilation has continued for 6–10 hours, cold blocking the carotid sinus nerve no longer has an

effect on respiration, and hyperventilation continues after restoration of normal oxygen tension to the animal. In the period of acute hypoxia, ventilation is increased by reflex drive of the anoxia; after a period of time the same or nearly the same volume of ventilation is needed for elimination of CO_2 and the respiration is again controlled by the response of the respiratory center to CO_2. The volume of ventilation is now sustained at a level sufficient to hold the CO_2 tension at low level because the bicarbonate concentration of the brain and central nervous system are reduced, and a rise in CO_2 tension above that established during the period of the anoxia chemoreceptor drive results in acidosis.

Observations on patients show, at times, continued hyperventilation in the face of a rising blood pH. This might be expected if the HCO_3^- concentration of the central nervous system lagged behind that of the blood. Experimental observations indicate that this may be so.

In patients with cyanotic congenital heart disease, chronic overbreathing is present. This can be detected by direct measurement of ventilation. The patients with congenital heart disease show less depression of bicarbonate than do subjects at high altitude, and their arterial pH is usually in normal range. The fall in pulmonary vein CO_2 tension caused by the overbreathing is balanced to a large extent in the arterial blood by the mixing of the overventilated blood with the venous blood shunted from the right to the left side of the heart.

Patients with dyspnea from congestive failure frequently have mild respiratory alkalosis. Because of the increased volume of ventilation, the alveolar oxygen tension tends to be high but, because of the lung disease produced by the congestion, the arterial oxygen tension tends to be depressed. This causes only minor changes in oxygen saturation and it is usually felt that they are too small to account for the overbreathing on the basis of an anoxic drive. Two facts make me believe that the change in oxygen tension may be of importance in the overbreathing. If the

ventilation volume is reduced to normal by the administration of morphine, obvious arterial unsaturation occurs. The oxygen tension of arterial blood in these subjects approaches the normal because of the increased ventilation. Secondly, changes of oxygen tension of a magnitude which cause little change in ventilation in a normal subject may cause a large change in ventilation in a dyspneic patient with congestive failure.

Patients with pulmonary alveolar capillary block may have a low CO_2 tension because of overbreathing. In water and tissues, CO_2 diffuses much more rapidly than does oxygen. For this reason, carbon dioxide retention does not occur with alveolar pulmonary capillary disease. It does occur when alveolar ventilation is reduced and the air in the alveoli is not readily mixed with the inspired air. Overbreathing in which the perfused alveolus is well washed leads to loss of CO_2 through the alveolar pulmonary capillary wall, even though the arterial oxygen may be greatly depressed because of the difficulty in O_2 diffusion through those same alveolar pulmonary capillary walls.

USES OF HYPERVENTILATION IN EXAMINATION

Patients who are hyperventilating may complain of (1) shortness of breath and (2) symptoms from CO_2 loss. The patients with shortness of breath can be divided into two groups: (a) those who do not increase their breathing beyond the normal range on exercise and (b) those who do overbreathe on exertion.

The patient may be conscious of normal respiration and therefore complain of dyspnea. He does not develop alkalosis with exercise and will not overbreathe voluntarily at a rate which produces a significant degree of alkalosis.

Many patients do have excess stimulation of ventilation at rest or when performing light exercise. They develop the symptomatology that goes with a loss of CO_2 which may go to the point of tetany. This may or may not be associated with overt anxiety. The hyperventilation may occur only during certain periods of

emotional stress or it may be brought on during exercise. Acute attacks of hyperventilation may happen at night, frequently occurring on awakening from a frightening dream. The dyspnea may cause the patient to sit up in bed and open the window for air. He is usually conscious of the tingling and lightheadedness caused by the loss of CO_2. These patients frequently complain of chills during the attack. They may realize that this type of chill is not followed by fever. These nocturnal attacks must be differentiated from paroxysmal nocturnal dyspnea from left ventricular failure. When the patient has normal lungs and a normal heart, the matter is simple; but if he has heart disease then the matter is more complex. Sometimes only extended observation will tell whether the patient is having an anxiety attack because of his fear of heart disease or is having an actual attack of pulmonary edema. The greater the signs of CO_2 loss, the more likely it is that anxiety is the major factor. In borderline patients the anxiety attack itself may precipitate pulmonary edema, and dyspnea from pulmonary edema certainly precipitates symptoms of overt anxiety.

Hyperventilation may be the chief symptom in early primary pulmonary hypertension. The dyspnea is restricted to effort, and is frequently associated with syncope. The ventilatory function of the lungs in these patients may be normal. In those patients with normal alveolar ventilation, slight exertion causes marked dyspnea with a rise in alveolar oxygen tension and a fall in alveolar CO_2 tension. The arterial blood shows an increase in oxygen tension and a decrease in CO_2 content, with a rise in pH. The alkalosis may be marked because the overbreathing is intermittent and the relatively normal alveoli are being perfused by a reduced quantity of blood. The rise in lactic acid which occurs in other forms of alkalosis is also seen here. The accentuated P_2, increased activity of the right ventricle on palpation, and the electrocardiographic pattern of right ventricular hypertrophy make one realize that an intractable and destructive illness is present. In other patients, the disease process has involved the alveoli and the capillaries, and

both ventilation and diffusion across the alveolar pulmonary capillary membranes may be impaired.

Many patients with hyperventilation do not complain of dyspnea. They note feelings of lightheadedness, unreality, numbness, tingling, coldness and carpopedal spasm. It is useful to try out three simple maneuvers in patients with vague complaints relating to consciousness: (1) pressure on each carotid sinus with the patient sitting, (2) effects of motionless standing with particular attention to pulse, blood pressure and respiration and (3) effect of a 2-minute period of voluntary hyperventilation. The hyperventilation may reproduce some of the patient's symptomatology. It may not reproduce any of the specific symptomatology, but one learns in a general way how the patient reacts when strange sensations occur in his body.

It has long been recognized that patients with spontaneous or exercise-produced hyperventilation have irritable nervous systems. The fact that the respiratory center does not slow down respiration when enough CO_2 has been lost to produce alkalosis is a sign of incoordination in the regulation of respiration. The patient may be taught to recognize the symptoms of hyperventilation and he may prevent them by breathing into a closed container, as a paper bag, but he will not recover normal smooth control of respiration unless the nervous system functions more normally. He can learn to understand his symptoms and tolerate them and be interested in the situations producing them, but this will not prevent uneven respiratory regulation in times of stress.

The patient with this kind of symptomatology is usually telling the physician two things: (1) his sensory nervous system is unusually sensitive to changes in environment so that changes commonly ignored are now noticed and (2) homeostatic regulation is poor so that swings in the internal environment are greater than normal. Both are responsible for a rather diffuse symptomatology. Examination of the patient shows that he has many evidences of poor homeostatic control. He has cold hands and feet,

he sweats profusely in certain areas, goose flesh appears and disappears, and the blood pressure rises too high at times and frequently falls more than expected under the stress of standing. History confirms irregular function of the gastrointestinal tract and the bladder, and difficulty in sexual activities. The laboratory shows both high and low concentrations of blood sugar, the cholesterol varies and the electrocardiogram is unstable.

The physician is likely to attribute the symptoms to the area of his own greatest interest. If he is studying the phenomenon of hyperventilation, this will be the diagnosis. If he is interested in blood sugar regulation, he will believe that he has an instance of functional hypoglycemia. If he is interested in postural reactions, he will attribute considerable importance to the fall in pressure on standing. If he is a gastroenterologist, he will be struck by many similarities between his patient and the "dumping syndrome." If he is a cardiologist, he will be intrigued by the changing electrocardiographic pattern. Because of the dyspnea, and the marked changes in pulse rate, he will summarize his impressions by the diagnosis of "effort syndrome."

In time, the physician is impressed with how little the basic complaint is helped by attention to one aspect of this diffuse disturbance, and he realizes that the patient is describing his over-all problem in sensory pickup and regulation of body function, and not a specific disturbance in a single function. He then needs to know what do doctors know about this type of illness and what is its course.

Some persons are born with a sensitive nervous system in which impulses "sprangle" (a fine Carolina term), and in which most sensory impulses cause widespread motor discharges. These patients may always be conscious of their body and the changes in their internal environment. Once they learn about their makeup, they should approach the doctor with the question: "Are these sensations disease or is this I?" Both patient and doctor have to recognize the biologic organization of these particular patients and not be irritated because it differs from others.

The organization of the nervous system and its ability to regulate the internal environment varies greatly in a given person (and, remember, he is different from all other persons) from time to time. The degree to which the system is capable of standing stress without breaking down is a measure of the stability of the system. The system may break down because (1) the stress has become too great or (2) the system is less capable of standing the same stress. By stress, we mean any load, physical, emotional, mental or social which requires additional activity in the mechanisms stabilizing nervous activity and internal environment of the body. By changes in the system, we mean any disturbance in cell function—be its etiology viral, bacterial, toxic, physical trauma, heat, cold or other physical agents; or caused by alteration in function of the nervous system from emotional or psychic reactions to the environment.

Many changes in the biology of the patient may occur which are not obvious when the organism is under minimal stress. If we wish to determine the presence of change we must find out if the ability of the organism to stand stress has changed. The stress does not in itself produce the disease, but it does make its presence obvious. A man with moderate coronary disease may have no angina during a relatively sedentary existence. Sudden heavy exertion may produce angina. The exercise has not produced coronary disease. It has merely demonstrated its presence. A patient in his forties may develop urticaria in certain situations in which he never before had difficulty. These situations, which formerly did not end in urticaria, do not produce the biologic changes responsible for the appearance of urticaria, but they do demonstrate that these biologic changes have occurred in the organism. From a practical point of view, the patient needs to know what situations he must avoid in view of the changes in his body.

The fact that patients are able, by their wide testing of themselves in the stresses of living, to find out that their bodies have changed when all of the physician's laboratory findings show no

change is not surprising. The patient is reporting the results of a series of biologic assays, and we know from experience that many biologic assays have a sensitivity far beyond that of our present chemical methods. In addition to his difficulty, we do not know all of the active ingredients of any biologic system. Therefore, it is not surprising that the patient describes to us symptoms that we do not understand.

Our knowledge of the symptomatology produced by discrete lesions in the nervous system is still in its infancy. As one watches the changes which occur in an aging population, it is clear that many of their reactions are determined by central nervous system disease. Many of the mechanisms of homeostasis which are reversibly disturbed in the person without destructive disease in the nervous system are permanently crippled in patients with destructive changes in the nervous system. In the early stages of destructive illness, symptomatology may be diffuse and hyperventilation may be present. Only a long follow-up will determine the kind of illness we are dealing with.

Patients with problems in homeostasis who have symptoms in part from hyperventilation may be grouped as follows:

1. Persons born with sensitive sensory systems and more widespread motor discharges than occur in the average person. These people will always have wide swings in internal environment and in symptomatology. The degree of symptomatology will parallel the physical, emotional, social and economic forces to which they are submitted. The doctor recognizes that these patients are different from the norm, and he teaches them to be tolerant of their bodies. The patient learns what situations provoke undue symptomatology and avoids them.

2. Persons with good homeostatic mechanisms in whom the load becomes too great for the homeostatic mechanisms functioning at a level commonly found in the population. In some way, the load must be lightened.

3. Persons who normally have carried the stress of living with-

out difficulty but who, because of a well-defined illness, can no longer manage the situation. We see this in infections, hepatitis, thyrotoxicosis, pernicious anemia and all other illnesses. Given time, these patients return to their former baseline, provided the precipitating disease can be controlled. Until the usual resiliency returns to the body, additional protection is needed.

4. Persons who can date the time when the body changed to a state of increased sensitivity in the sensory and motor systems. A history of previous episodes in the patient or family is common. At some unpredictable time the patient reverts back to his more normal state. We usually describe these as episodes of self-circumscribed illness characterized by fatigue, depression, loss of sexual drive, unusual sensitivity of the nervous system and poor regulation of the internal environments. Because they feel so bad, many of these patients say that they are carrying heavy loads. The loads certainly seem heavy to the patient, but objective evidence to this effect may not be found. Many of these patients feel quite desperate. They project the future in terms of the present and feel that some organic treatable disease must be found or they will not be able to continue living. The doctor has the great advantage of knowing that the patient will improve in time even if nothing is done. He can help the patient live through the present without anxiety because he knows that the future is not a projection of the present. The doctor uses whatever symptomatic therapy is needed until recovery occurs. He advises the patient against making decisions which will cause large changes in his pattern of living until he feels well again. He uses whatever symptomatic therapy is needed for the patient and himself to live until recovery occurs.

5. Patients with destructive organic disease without localizing signs. This can range from cerebrovascular disease to diffuse carcinomatosis.

6. Patients with a major psychosis may pass through this stage of diffuse irritability of the nervous system.

OTHER DISEASE STATES CAUSING RESPIRATORY ALKALOSIS

Respiratory alkalosis is seen in intoxication with sulfanilamide, salicylate and dinitrophenol. In salicylate intoxication, respiratory alkalosis is followed by metabolic acidosis. During the period of respiratory alkalosis, potassium is lost from the body and electrocardiographic changes suggesting a fall in serum potassium and areflexia may occur. These changes are reversed by potassium. The urine in salicylate intoxication may be acid in the face of respiratory alkalosis. The shift from respiratory alkalosis to respiratory acidosis may be rapid and will be detected only by following the pH of arterial blood.

Patients with hepatic disease show respiratory alkalosis. Tyor and Sieker, in a group of 18 normal subjects, found a mean arterial pH of 7.38 and a CO_2 tension of 44.6 mm. of Hg. Patients with severe liver disease but no detectable abnormality in mental function had a mean arterial pH of 7.42 and a CO_2 tension of 37.5 mm. of Hg. Patients with stupor or coma from hepatic disease had an average arterial pH of 7.42 and a CO_2 tension of 31.8 mm. of Hg.

The treatment of respiratory alkalosis by inhalation of air containing sufficient CO_2 to lower the pH to normal levels has not been helpful in patients with cirrhosis or salicylate intoxication. These patients do not have symptoms directly related to respiratory alkalosis and, therefore, obtain no symptomatic relief from breathing in a partially closed container or increasing the concentration of CO_2 in inspired air by other means.

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